Decline of EMRSA-16 amongst methicillin-resistant Staphylococcus aureus causing bacteraemias in the UK between 2001 and 2007

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Objectives: Between 1998 and 2000, 95.6% of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemias in the UK were due to two epidemic strains, namely EMRSA-15 or EMRSA-16 (60.2% and 35.4%, respectively). We sought to determine the proportions of these strains before and after the general decline in MRSA bacteraemia that began around 2004.

Methods: Consecutive MRSA isolates collected in 2001, 2003, 2005 and 2007 by the BSAC Bacteraemia Surveillance Programme were categorized to multilocus sequence typing (MLST) clonal complex and to SCCmec type by PCR. MICs were determined by the BSAC method. Data trends were tested for significance using a generalized linear regression model.

Results: Collectively, EMRSA-15 and EMRSA-16 consistently accounted for ~95% of MRSA studied between 2001 and 2007, but the proportions of EMRSA-16 declined from 21.4% in 2001 to 9% in 2007 (P<0.05), whilst the proportion of EMRSA-15 rose commensurately, accounting for 85% of MRSA in 2007. Ciprofloxacin and erythromycin resistance were common amongst both EMRSA-15 and EMRSA-16.

Conclusions: EMRSA-15 and EMRSA-16 remain the main MRSA strains in bacteraemia in the UK, but the proportion of EMRSA-16 declined from the late 1990s, thus preceding the general decline in MRSA bacteraemias that began in the middle of the present decade.

Keywords: MRSA, surveillance, bloodstream infections

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) emerged in 1961 and became dramatically more prevalent as agents of bacteraemia in the UK in the mid-1990s in England, Wales and Northern Ireland. By the end of the 1990s, >40% of all St. aureus bacteraemias were due to MRSA, though this proportion (and the total number) of MRSA bacteraemias has since declined and stood at ~20% in 2008.1 The rise of MRSA in the 1990s and early 2000s correlated with the emergence and spread of two epidemic strains, designated EMRSA-15 and EMRSA-16, which, in 1999–2000, accounted for 95.6% of all UK MRSA bacteraemias; with 60.2% due to EMRSA-15 and 35.4% to EMRSA-16.2

EMRSA-15 and EMRSA-16 differ genetically, belonging to distinct multilocus sequence type (MLST) clonal complexes (CCs), namely CC22 (ST22) for EMRSA-15 and CC30 (ST36) for EMRSA-16.3 They also differ in their staphylococcal cassette chromosome mec (SCCmec) types, with EMRSA-15 typically harbouring SCCmecIV whereas EMRSA-16 typically has SCCmecII.4 They may differ in resistance profile too, but both lineages are usually resistant to fluoroquinolones and macrolides, and the use of these antibiotics has been described as a risk factor for colonization or infection.5 Since its first emergence in the UK, EMRSA-15 has become disseminated in Europe,6 Australia,7 the Middle East8 and the Far East;9 EMRSA-16 has been reported widely, in- and outside of the UK, but it is not perceived to be as successful as EMRSA-15.

Here, we report trends for EMRSA-15 and EMRSA-16 among MRSA isolated as part of the BSAC Bacteraemia Surveillance Programme between 2001 and 2007.

Materials and methods

Bacterial isolates and collecting centres

The methods for the BSAC Bacteraemia Surveillance Programme (http://www.bsacsurv.org) have been described previously.10 In brief, 25 clinical
EMRSA-16 R.I.P.?

Table 1. EMRSA-15, EMRSA-16 and other strains amongst BSAC MRSA Bacteraemia Surveillance Programme isolates collected in 2001, 2003, 2005 and 2007

<table>
<thead>
<tr>
<th>Survey year</th>
<th>EMRSA-15 n</th>
<th>proportion of all MRSA (%)</th>
<th>EMRSA-16 n</th>
<th>proportion of all MRSA (%)</th>
<th>Other strain(s) n</th>
<th>proportion of all MRSA (%)</th>
<th>Total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>78</td>
<td>75.7</td>
<td>22</td>
<td>21.4</td>
<td>3</td>
<td>2.9</td>
<td>103</td>
</tr>
<tr>
<td>2003</td>
<td>70</td>
<td>73.7</td>
<td>20</td>
<td>21.1</td>
<td>5</td>
<td>5.3</td>
<td>95</td>
</tr>
<tr>
<td>2005</td>
<td>71</td>
<td>81.6</td>
<td>12</td>
<td>13.8</td>
<td>4</td>
<td>4.6</td>
<td>87</td>
</tr>
<tr>
<td>2007</td>
<td>76</td>
<td>85.4</td>
<td>8</td>
<td>9.0</td>
<td>5</td>
<td>5.6</td>
<td>89</td>
</tr>
<tr>
<td>Total</td>
<td>295</td>
<td>62</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td>374</td>
</tr>
</tbody>
</table>

Laboratories in the UK and Ireland, serving a wide range of urban and rural areas with a range of social deprivation scores, contributed isolates in each year. A total of 29 centres participated during 4 study years (2001, 2003, 2005 and 2007) and 17 of these submitted isolates in all 4 years; the remainder either joined or left the programme between 2001 and 2007. All MRSA isolates collected in the 4 years (n=103 from 2001, n=95 from 2003, n=87 from 2005 and n=89 from 2007) were investigated. To match with MRSA mandatory surveillance data, some analyses considered only the isolates collected in hospitals in England. These comprised 85 in 2001, 76 in 2003, 71 in 2005 and 70 in 2007, from a total of 23 centres, of which 15 participated in all 4 years of the study. The mandatory MRSA bacteraemia surveillance system, which applies to England only, was first introduced in 2001 and has recently been described in detail.1

Susceptibility testing
MICs were determined on Iso-Sensitest agar (Oxoid, Basingstoke, UK), according to the BSAC method.5 The antimicrobial agents tested were obtained as described previously.10

Molecular detection of CC and SCCmec cassette type
Previously described PCRs were used to detect the SCCmec type11,12 and the S. aureus CC-specific marker hsdR,13 thus differentiating CC22-MRSA-SCCmecIV (corresponding to EMRSA-15) and CC30-MRSA-SCCmecI (corresponding to EMRSA-16).

Data analysis
Regression analysis using the generalized linear model with Poisson distribution was performed via STATA version 10.1 (Statacorp, 2008).

Results and discussion
A total of 374 MRSA were analysed, and throughout the years 2001, 2003, 2005 and 2007, ~95% of the isolates were found to be either EMRSA-15 or EMRSA-16. Among the 29 centres that submitted isolates, all submitted EMRSA-15, whilst 22/29 submitted EMRSA-16, illustrating geographic dissemination of both strains. Nevertheless, the proportion of EMRSA-16 declined from 21.4% in 2001 to 9% in 2007, whilst an increase occurred in the proportion of EMRSA-15, from 75.7% in 2001 to 85.4% in 2007 (P=0.014) (Table 1). These data corroborate previous local and national observations of a general decline in EMRSA-16.4,12 but do not preclude the possibility of localized variance from this trend. Consideration of previous (phage-type based) data for isolates collected between 1998 and 2000 under the aegis of the European Antimicrobial Resistance Surveillance Study indicated a 14% decline in EMRSA-16, from 35.4% seen in 1998–20002 to the present start point of 21.4% in 2001, and a subsequent decline to 9% in 2007. Whilst these data span different collections and methods, they support the view that the relative and absolute decline of EMRSA-16 began before the plateau and decline in total MRSA bacteraemias seen through the results of the mandatory surveillance system.1

As noted previously, the majority of both EMRSA-15 and EMRSA-16 isolates were resistant to macrolides (74% and 85%, respectively) and fluoroquinolones (97% and 95%, respectively), whilst gentamicin resistance was noted in 3% and 24%, respectively. Resistance to tetracyclines was rarer (3% in both strains). Susceptibility to mupirocin was determined only from 2007. Among subsequent isolates, we found 1/8 (13%) EMRSA-16 and 2/76 (3%) EMRSA-15 to be highly resistant (MICs > 256 mg/L).

In summary, the trends observed here suggest that EMRSA-15 and EMRSA-16 have followed different epidemic curves, with EMRSA-16 having peaked and declined earlier than EMRSA-15, and with each then contributing differentially to the total MRSA bacteraemia rate, which peaked in 2004 and declined thereafter. Whilst the reason(s) for the selective decline of EMRSA-16 are not known, various factors, and possible combinations, warrant consideration, including antibiotic prescribing patterns, infection control measures and various possible biological drivers, such as bacteriophage epidemics. It remains to be seen whether the downward trajectory of EMRSA-16 will continue and if EMRSA-15 will remain the dominant MRSA lineage associated with invasive disease in hospitals in the UK.

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References